UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation **This Document Related To: All Cases**	**22md3043 (DLC)**

PLAINTIFFS' OPPOSITION TO DEFENDANTS' MOTIONS TO EXCLUDE EXPERT TESTIMONY OF ROBERT M. CABRERA, Ph.D.

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INTRODUCTION

Defendants can only challenge Dr. Robert Cabrera's testimony by distorting the law and misstating the facts. Dr. Cabrera is a world-renowned teratologist who painstakingly analyzed the relevant preclinical (animal), epidemiological, and mechanistic evidence employing a weight-of-the evidence methodology and the Adverse Outcome Pathway (AOP) framework. His thorough report details why the evidence shows that prenatal exposure to therapeutic doses of APAP causes ASD and ADHD in offspring.

While Defendants do not like that damning conclusion, it is black-letter law that the Rule 702 inquiry "must focus on the [expert's] principles and methodologies," *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 267 (2d Cir. 2002), not the conclusions they produce. Dr. Cabrera's principles and methodologies are beyond reproach. They are the exact same principles and methodologies that Dr. Cabrera applies in his daily work as a diligent scientist. They are the exact same principles and methodologies that teratologists around the world routinely employ.

Unable to lodge a *legitimate* methodological critique, Defendants incant methodological jargon in hopes of masking what is at bottom an impermissible attack on Dr. Cabrera's ultimate conclusions. The maneuver first proceeds by claiming that Dr. Cabrera must be "cherry picking" the evidence he reviewed because he does not accept the putatively inexorable fact that genes are the sole cause of ASD and ADHD. Dr. Cabrera—and indeed all of Plaintiffs' experts—reject that premise not because they are "cherry picking," but because it is categorically false.

Outside of litigation, Defendants' own experts agree with Dr. Cabrera and the rest of the scientific community: Genes interact with the environment to cause ASD and ADHD. *See, e.g.*, Ex. 178, Chung SPARK Presentation Audio ("These genetic factors in some individuals can be an important cause of autism but it's certainly not the only cause that we see of autism. . . . And in fact there's probably a complex interplay between both the genes as well as these exposures.");

Ex. 93, Faraone (2021) at 792 tbl.1 ("[M]ost cases of ADHD are caused by the combined effects of many genetic *and* environmental risks.") (emphasis added); Ex. 28, Kolevzon Dep. Tr. at 368:11–19 (discussing his 2021 paper describing "[t]he etiology of ASD" as "multifactorial" including "genetic and environmental factors, as well as their interaction"). Here, the environmental trigger is prenatal exposure to APAP, and it is no defense to claim that genes are also a but-for cause of the Plaintiffs' injuries. *See* Dkt. 1138 at 12–13 (citing Restatement (Third) of Torts § 26 cmt. c).

Defendants next accuse Dr. Cabrera of ignoring key limitations in the epidemiological literature. That false charge is easy to debunk. Dr. Cabrera's painstaking analysis described the strengths of studies that do not support his position and the limitations of studies that do. He did not ignore any evidence. He simply weighed it in a way that Defendants do not like. Under Rule 702, they must present their counterweighting to a jury. Defendants also repeat their non sequitur that animals are not people, so any consideration of animal studies is somehow verboten. Outside of litigation, no teratologist accepts that narrow view. JJCI and FDA do not either. Particularly where randomized clinical trials in humans would be unethical, it is standard practice to evaluate preclinical lines of evidence to reinforce the inferences drawn from observational epidemiology. That is precisely what Dr. Cabrera did, fortifying his opinion that the link between APAP and ASD/ADHD is causal.

Finally, Defendants consistently misstate the Bradford Hill factors. For instance, Defendants claim biologically "plausible" means biologically *established*, rendering Dr. Cabrera's well-reasoned candidates for the biological mechanisms by which APAP causes neurodevelopmental disruption "wildly speculative." Defs. Mechanism Br. at 1, Dkt. 1165. But Rule 702 does not appoint Defendants as Sir Bradford Hill's lexicographer. Plausible means

"possible" or "credible," not established. *See* Ex. 25, Pinto-Martin Dep. Tr. at 542:22–25. The mechanisms Dr. Cabrera analyzes meet the proper definition. For instance, barrels of peer reviewed ink have been spilled since the 1970s showing that APAP can cause oxidative stress. Ex. 3, Cabrera Rep. at 39. And a simple search of PubMed shows that "oxidative stress and autism" yields 883 results, the first of which was published in 2002. Substituting ADHD for autism yields 193 results going back to 2000. It is therefore no surprise that many independent scientists in peer reviewed publications have identified the same biologically plausible mechanisms that Defendants dismiss as "wildly speculative." Defs. Mechanism Br. at 1.

Defendants' best argument—acknowledged by their own experts—is that reasonable scientists are engaged in a debate about acetaminophen. Those are not grounds for exclusion under Rule 702. And, critically, depriving pregnant women of vital, well-grounded scientific opinions that injudicious use of acetaminophen poses grave risks to their children. Dr. Cabrera undertook a methodologically sound, exacting analysis of the preclinical and epidemiological literature to reach his conclusions. The motion to exclude his testimony must be denied.

BACKGROUND

I. Dr. Cabrera Is Eminently Qualified.

Dr. Cabrera is an Associate Professor in Molecular and Cellular Biology at Baylor College of Medicine and an Adjunct Professor of Biology at San Jacinto College, where he runs the Finnell/Cabrera Birth Defects Research Laboratory. Ex. 22, Cabrera Dep. Tr. at 388:3–8; Ex. 3, Cabrera Rep. at 3. Dr. Cabrera specializes in teratology, which is "the scientific study of abnormalities, malformations, and developmental disorders that occur during prenatal development." *Id.* As a teratologist, Dr. Cabrera's "bread and butter" is "looking at particular chemical exposures, and then we look for what's called gene environment interactions" or "particular changes in genetics that increase the risk for an adverse outcome with an exposure."

Ex. 22, Cabrera Dep. Tr. at 390:12–21. Dr. Cabrera is a principal investigator at the National Institute of Health (NIH) and leads NIH-funded research. Ex. 3, Cabrera Rep. Ex. A at 1; Ex. 22, Cabrera Dep. Tr. at 388:21–389:6. He "actively conduct[s] and participate[s] in human epidemiology and animal teratology studies that focus on determining the mechanisms of birth defects." Ex. 3, Cabrera Rep. at 5. Prior to his current appointments, Dr. Cabrera was an Instructor at Concordia University, the Manager for Stem Cell Research at the Dell Pediatric Research Institute, and a Faculty Lecturer and Research Scientist at the University of Texas at Austin. *Id.* at 3. He has over 20 years of experience studying and researching chemicals to assess developmental toxicity and potential risk factors for birth defects. *Id.*; *see also* Ex. 3, Cabrera Rep. Ex. A at 1.

Dr. Cabrera has written over three dozen peer-reviewed scientific research articles. *Id.* at 3–6. For example, he studied neural tube defects in mouse models "to examine the impact of altering the normal pattern of gene expression in the developing neural tube."[1] He studied the etiology of neural tube defects and "how teratogens can perturb these orchestrated processes."[2] He also studied "birth defects in expectant mothers" using the large population-based Norwegian Mother and Child Cohort Study and the Danish National Birth Cohort Study, [3] both of which have been used in research relating to APAP and neurodevelopmental disorders. Ex. 3, Cabrera Rep. at 4. He has also written textbook chapters on "the use of functional genetics in developmental toxicity testing." *Id.* at 5.

[1] Richard H. Finnell et al., *Gene Expression Profiling Within the Developing Neural Tube*, 27 Neurochem. Res. 1165, 1165 (2002).

[2] Robert M. Cabrera et al., *Investigations Into the Etiology of Neural Tube Defects*, 72 Birth Defects Res. Pt. C: Embryo Today 330, 330 (2004).

[3] Abee L. Boyles et al., *Association Between Inhibited Binding of Folic Acid to Folate Receptor Alpha in Maternal Serum and Folate-Related Birth Defects in Norway*, 26 Human Reproduction 2232 (2011) (using Norwegian Birth Cohort); Camilla Bille et al., *Autoantibodies to Folate Receptor Alpha During Early Pregnancy and Risk of Oral Clefts in Denmark*, 67 Pediatric Res. 274 (2010) (using Danish Birth Cohort).

II. Dr. Cabrera's Methodology and Opinions

To prepare his report, Dr. Cabrera conducted a "comprehensive literature search" including "primary reports from animal model testing and epidemiology studies." *Id.* at 7. The result was a 196-page, single-spaced, report providing an in-depth analysis of relevant preclinical (animal), epidemiological, and mechanistic evidence using weight-of-the evidence principles, the AOP framework, and the Bradford Hill causation analysis. Dr. Cabrera's "integration of animal and human data . . . is necessary" given the ethical concerns preventing the testing of APAP in pregnant women. *Id.* at 13. But in weighing each line of evidence (*i.e.*, animal research or human cohort studies), Dr. Cabrera considered the "hierarchy of evidence," recognizing that animal studies offer less relevant "evidence to human health benefits or risks" while systematic reviews and meta-analyses offer the most relevant evidence. *Id.* at 13 fig.1.

A. Weight of the Evidence

Dr. Cabrera's opinions are based on his detailed review of 87 animal model studies and 46 human epidemiological studies. *See id.* at 80–118 (discussing animal studies); *id.* at 128–75 (discussing epidemiology). He applied "six [q]uality [a]ssessment [p]oints" to integrate the animal and human evidence and weigh each study. *Id.* at 15–16. Following a study-by-study analysis, Dr. Cabrera rated the findings of each study according to the National Toxicology Program's rating guidelines that set out five "levels" ranging from "clear evidence of developmental toxicity" to "inadequate study of developmental toxicity." *Id.* at 124.

1. Animal Studies

"When assessing whether a drug exposure causes an adverse outcome, animal studies can provide important evidence that cannot be obtained from human subjects." *Id.* at 76. Scientists are able to extrapolate animal model results to learn about how exposures might affect humans because "[t]he physiological systems of mammals depend on common and conserved genetic,

cellular, and tissue processes." *Id.* Both species "undergo rapid brain development *in utero* and after birth" and "there is shared underlying brain architecture in all regions of the brain." *Id.* at 76-77. Animal models are also particularly useful here because "both humans and rodents metabolize APAP using homologous enzymes that result in the same metabolites being produced." *Id.* at 76. In evaluating specific adverse outcomes in animal models, scientists use well-established behavioral tests that correspond to analogous human behavioral symptoms, such as hyperactivity or anxiety, as well as biological measures, such as neuroanatomy and epigenetics. *Id.* at 77.

Dr. Cabrera reviewed animal studies that examine the influence of APAP exposure on neurobehavioral changes, neurobiological damage, glutathione depletion, toxicity from oxidative stress, and changes in reproductive and other tissues in mice, rats, and hamsters. *Id.* at 80–118. For each study, Dr. Cabrera identified the animal "strain" and APAP dosages used, *id.* at 81–82 tbl.6, 98–99 tbl.9, and provided a study-by-study analysis detailing key findings. Numerous study authors expressly conclude that their results raise concerns about the use of APAP during pregnancy. *See, e.g.*, Ex. 180, Hay-Schmidt (2017) at 2, 14; Ex. 181, Hurtado-Gonzalez (2018) at 14; Ex. 182, Philippot (2018) at 203, 210; Ex. 167, Rigobello (2021) at 5; Ex. 183, Koehn (2020) at 26. But the findings were not without limitations, as Dr. Cabrera notes. For example, in his discussion of Klein (2020), he acknowledged some findings showed that APAP did *not* impair certain biological and behavioral measures. Ex. 3, Cabrera Rep. at 102. He similarly noted that a study showing "acetaminophen was associated with a significant increase in . . . asocial behavior" did *not* measure "oxidative stress, glutathione, or products produced by NAPQI." *Id.* at 103 (describing Suda et al. (2021)). The only APAP study in hamsters described in his report resulted in a "significant dose-responsive teratogenic response," but Dr. Cabrera acknowledged this result "lack[ed] replication." *Id.* at 117 (describing Rutkowski & Fermm (1982)).

Following his study-by-study review, Dr. Cabrera offered "conclusions . . . based on applying the weight of evidence (WoE) to the Oxidative Stress Adverse Outcome Pathway (AOP) that identifies APAP as a stressor." *Id.* at 124. In particular, he identified 22 animal model studies that provided "clear evidence" (under the National Toxicology Program's guidelines) "of developmental toxicity, with oxidative stress and oxidative DNA damage, consistent with developmental neurotoxicity due to perinatal APAP exposure." *Id.* at 125–26. In addition, out of 17 studies evaluating the association between APAP exposure and learning or social behavior, 14 reported "clear evidence" that APAP impairs such behaviors. *Id.* at 126–27. Finally, Dr. Cabrera reported "over 90% of the studies" he reviewed "support[] the hypothesis that APAP exposure during neurodevelopment at doses equivalent to therapeutic human doses causes significant changes in the brain and results in significant behavioral effects later in life." *Id.* at 128.

2. Human Studies

"[T]he scientific literature also supports increased risk of neurodevelopmental toxicity in humans associated with APAP exposure during pregnancy." *Id.* at 128. Dr. Cabrera conducted a comprehensive review of all relevant epidemiological studies, which he sorts into six categories: (1) ASD, (2) ADHD, (3) impaired learning, cognitive, or social outcomes, (4) birth outcomes, (5) meta-analyses, and (6) other relevant reviews. *Id.* The scope of his review was determined based on the "overlap in presentation and etiology" between ADHD and ASD, as recognized by the fifth edition of the Diagnostic and Statistical Manual ("DSM-5"). Ex. 8, Cabrera Rebuttal Rep. at 2; *see also* Hollander Opp'n at 6–14 (describing the merits of the transdiagnostic approach in greater detail).

Dr. Cabrera reviewed each category of literature separately *and* in combination. He identified key features of each study, including the data source for exposure and outcome, controls,

study size, confounders, limitations, and results. *See, e.g.*, Ex. 3, Cabrera Rep. at 128–29 (describing Avella-Garcia (2016)).

Following his review, Dr. Cabrera evaluated the findings using the National Toxicology Program guidelines. Specifically, for each category of relevant evidence, he concluded that the epidemiological studies provide "some evidence" that APAP causes developmental toxicity. *Id.* at 134 (ASD), 146 (ADHD), 160 (other neurodevelopmental outcomes). The meta-analyses—"high-quality evidence" under the hierarchy of evidence—provide "clear evidence of developmental toxicity." *Id.* at 168. Thus, each category of literature independently supports a conclusion that there is a "moderate association" between prenatal APAP exposure and ASD, ADHD, and other adverse neurodevelopmental outcomes in children. *Id.* at 134 (ASD), 147 (ADHD), 160 (other neurodevelopmental outcomes), 168 (meta-analyses).

Dr. Cabrera highlighted several strengths and limitations of the epidemiological studies. For example, studies that used self-reporting as "the primary mode of determining APAP exposures" suffered potential misclassification bias, but such bias was not present in studies that used direct measures of APAP in fetal blood, such as Ji et al. (2020). *Id.* at 175. In addition, "certain factors identified as potential confounders that are controlled for in a study can be mediators or modifiers of toxicity." *Id.* Attempts to control for genetic confounders, for instance, can "mask the effects of genetic vulnerability" that "may not cause ASD or ADHD without additional environmental stress" such as prenatal exposure to APAP. *Id.* Ultimately, he concluded "the weight of the evidence indicates APAP has 'clear evidence' of developmental toxicity" and "[t]here are moderate associations between maternal use of APAP during pregnancy and an increased risk of ADHD and ASD in offspring." *Id.* at 175–76.

B. Bradford Hill Causation Analysis

Following his comprehensive, study-by-study analysis and weighing of the relevant scientific literature, Dr. Cabrera applies the Bradford Hill factors to assess whether causality can be inferred. *Id.* at 189–95. Dr. Cabrera explained each of the nine Bradford Hill criteria and identified specific evidence on which he based his assessment. He concluded, based on the totality of the evidence, the strength of association, consistency, temporality, biological gradient, biological plausibility, coherence, experimental evidence, and analogy factors are satisfied. *Id.* Only the specificity criterion was "not fully met" because "ASD and ADHD can also be caused by other exposures." *Id.* at 191. This analysis provided the basis for Dr. Cabrera's conclusion that "[t]herapeutic dosages of APAP taken by pregnant women are sufficient to cause neurotoxicity, neurodevelopmental disorder, ASD, and ADHD in exposed offspring." *Id.* at 196.

C. Adverse Outcome Pathways and Biological Mechanisms

Dr. Cabrera used the AOP framework to "understand the causal relationship between chemical exposures and adverse effects on living organisms," and set forth the biological mechanisms from the initiating molecular event to the effects on the organism phenotype. *Id.* at 18. AOPs are promulgated by the Organisation for Economic Cooperation and Development ("OECD") with input from international regulatory agencies, including the U.S. Environmental Protection Agency. Scientists use AOPs "to collect and connect biological information to create a fuller picture of how toxicity may be expressed in the body." Ex. 195, EPA AOP Database. "AOPs enable us to better use all existing information to evaluate" chemical toxicity. *Id.* This process involves organizing information about how a chemical progresses through the body causing cellular effects, organ effects, and, ultimately, individual and population-wide effects. Ex. 3, Cabrera Rep. at 18 fig.2; *see also id.* at 35 fig.11 (depicting the AOP relevant to APAP). Each AOP identifies "key events" in the path from chemical exposure (or "molecular initiating event")

to individual and population-wide effects. Each "key event" is "a measurable biological change at the molecular, cellular, or tissue level." Ex. 195, EPA AOP Database.

Applying the methodology "that was described in AOP [20], to come to the similar adverse events" of ASD and ADHD, Dr. Cabrera identified biological mechanisms showing how APAP can affect neurodevelopment. *See* Ex. 3, Cabrera Rep. at 9; Ex. 22, Cabrera Dep. Tr. at 326:20–327:1. In particular, Dr. Cabrera outlined how NAPQI, a toxic byproduct of APAP, creates oxidative stress and depletes the antioxidant glutathione ("GSH"), Ex. 3, Cabrera Rep. at 9, 43–47; how therapeutic doses of APAP produce the metabolite AM4040 and disrupt endocannabinoid signaling, *id.* at 9, 47–52; how APAP disrupts prostaglandins during brain development; *id.* at 52–53; and how APAP impacts vanilloid and serotonergic pathways, *id.* at 53–54. The biological mechanisms that Dr. Cabrera presented constitute a coherent and complete causal chain from the "molecular initiating event" (*i.e.*, APAP) to the individual and population-wide response (*i.e.*, ASD and ADHD). *See id.* at 38–73. Through this analysis, Dr. Cabrera lays out a clear causal chain showing that ingestion of APAP by pregnant mothers plausibly leads to ASD and ADHD in their children.[4]

As just one example, Dr. Cabrera lays out in detail the mechanism by which APAP causes oxidative stress within the developing brain, leading to disruptions in neuronal proliferation and differentiation, ultimately manifesting in ASD and ADHD. *Id.* at 43–47. His detailed analysis begins with the process by which APAP is metabolized in the human body. *Id.* at 38–39. He explains the specific route by which APAP crosses the placental barrier and reaches the fetal brain, avoiding liver metabolism in the fetus. *Id.* at 58.

[4] These mechanisms of action are described in more detail in Plaintiffs' Pearson Opposition at 4–10.

Dr. Cabrera's report goes on to explain that once present in the fetal brain, APAP is converted to its toxic metabolite NAPQI. *Id.* at 59–60. Far from being a "minor metabolite," Defs. Mechanism Br. at 2, NAPQI is in fact a toxic metabolite of APAP and a powerful biochemical oxidizer which has been known to cause organ toxicity since the 1970s. Ex. 3, Cabrera Rep. at 40. NAPQI is the reason APAP is responsible for almost half (46%) of liver failures in the United States. *See id.* at 19–20.[5] NAPQI causes damage by creating an imbalance of reactive oxygen species, a phenomenon known as oxidative stress. Citing peer-reviewed studies, Dr. Cabrera shows that a typical therapeutic dose of APAP "exerts oxidative stress and depletes glutathione in the brain," with increased damage resulting from increased duration and frequency of exposure. *Id.* at 64; *see also id.* at 42–43, 61–62. He shows that "the brain is particularly vulnerable to oxidative stress because it has high lipid content and limited antioxidant capacity." *Id.* at 64. He also shows the results of a peer-reviewed study demonstrating that APAP concentrations in the brain of the fetus are even greater—"concentrations were two to seven times higher in developing brains compared to adults," with increased concentrations for chronic use. *Id.* at 58. Dr. Cabrera shows that the oxidative stress balance is particularly important for the developing brain, because it is used as a signaling mechanism in developing cells to regulate proliferation (increasing the number of neurons from progenitor and stem cells) and differentiation (neurons developing into the different types). *Id.* at 63 fig.22.

When the delicate process of neuronal proliferation and differentiation is disrupted, the fetal brain can form "too many, too few, or the wrong type of cells to establish specific neural tracts and pathways." *Id.* at 68. Depending on timing and degree, altering oxidative stress balance

[5] When FDA finally proposed a warning to address liver failure, JJCI's predecessor vehemently opposed it. The arguments were eerily similar: a hepatoxicity warning was "unnecessary and serves only to confuse and frighten the vast majority of consumers who use acetaminophen in a rational and appropriate fashion." Ex. 75, Propublica (2013). If history does not fully repeat itself, it surely rhymes.

during neural development results in "increase[d] cell proliferation and therefore more neurons." *Id.* This is consistent with studies showing "areas of brain overgrowth in some individuals with ASD." *Id.* If, however, the timing of the disruption results in "premature differentiation," this would cause disorganization of cortical layers, which is consistent with the "patches of disorganization and functional disruption of neuronal tracts" found in children with ASD. *Id.* And altering differentiation of neurons (*i.e.*, altering the relative balance of neuron types, including dopaminergic neurons and noradrenergic neurons) is consistent with numerous animal studies presented by Dr. Cabrera demonstrating that prenatal APAP exposure result in offspring with altered levels of dopamine and noradrenalin. *Id.* at 125–26. The scientific consensus is that children with ADHD have dysregulated dopamine and noradrenalin systems, which can be treated by drugs targeting those systems. Ex. 196, Farone Dep. Ex. 771, at 5–6; Ex. 197, Faraone (2015) at 17 (stating that "current medications have dopaminergic or noradrenergic targets").

Dr. Cabrera cited AOP 20 as support for how prenatal use of APAP can cause ASD and ADHD in children through oxidative stress. *See* Ex. 3, Cabrera Rep. at 10, 35–36, 192, 194. As Dr. Cabrera explained, "one of the identified stressor chemicals for AOP 20 is [APAP], and the analysis concluded that exposure to these chemicals during 'brain development' may create 'oxidative stress' sufficient to 'cause cellular injury and death' that disrupts 'the establishment of neuronal connections and networks' and can 'lead to functional impairment in learning and memory.'" *Id.* at 35 (citing Ex. 184, AOP 20 (abstract)). Accordingly, AOP 20 "provides independent support for a causal relationship between APAP and the identified key events and adverse outcomes." *Id.* at 36.

LEGAL STANDARD

Plaintiffs refer the Court to the Rule 702 legal standard set forth in Plaintiffs' Baccarelli Opposition at 33–34.

ARGUMENT

I. Defendants Do Not Attack Dr. Cabrera's Weight of Evidence Methodology and Analysis.

A WoE analysis is a fundamental component of Dr. Cabrera's expert opinions. Defendants do not claim that this methodology is unreliable, nor could they. "Courts have found that the [WoE] methodology is scientifically acceptable because it is not intrinsically unscientific for experienced professionals to arrive at a conclusion by weighing all available scientific evidence—this is not the sort of junk science with which *Daubert* was concerned." *Daniels-Feasel v. Forest Pharms., Inc*., No. 17 CV 4188-LTS-JLC, 2021 WL 4037820, at *6 (S.D.N.Y. Sept. 3, 2021) (internal quotation marks omitted).

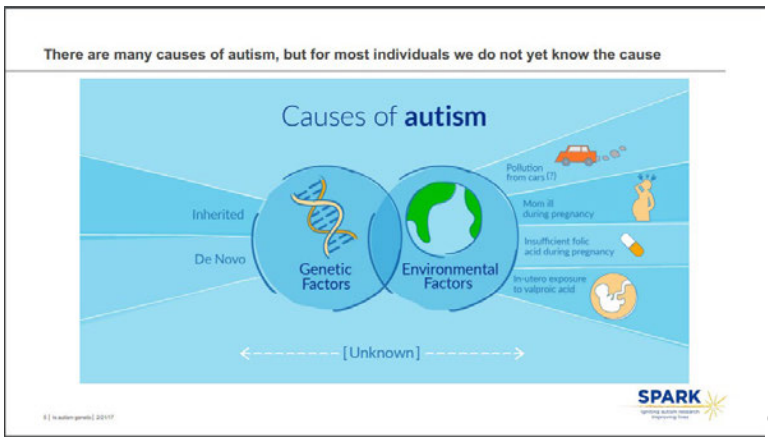
II. Dr. Cabrera Properly Accounted for Genetics.

From the very first line of Defendants' ASD brief to their arguments against each and every Plaintiffs' expert, Defendants declare to all and sundry that ASD and ADHD are caused by genetics alone. That defense is felled by a simple, universally recognized point: it is false. There is no question that genes play an important role in the presentation of ASD and ADHD. But so do environmental factors. Dr. Cabrera candidly acknowledges that scientific reality. Defendants do not. As Dr. Cabrera explained, "[t]he best approximation of scientific truth is not genetics alone, that is about as far from the truth as possible, other-than *the environment alone*. The best models for phenotype, epigenetic, or disease variability are and will remain gene-environment interactions for the foreseeable future." Ex. 8, Cabrera Rebuttal Rep. at 10 (emphasis in original).

A. Defendants' Genetics-Only Argument Is Premised on a Fundamentally Wrong Scientific Principle.

The very first line of Defendants' brief to exclude Dr. Cabrera reads: "Autism Spectrum Disorder ('ASD') has one known cause: genetics." *See* Defs. ASD Br. Dkt. 1160, at 1. Defendants' geneticist does not agree. At least when she is outside of litigation. In discussions to

lay and scientific audiences alike, Dr. Wendy Chung's prominently lists environmental factors, including "in-utero exposure to valproic acid," as "***causes*** of autism."



[6]

Dkt. 1138 at 15–18 (emphasis added). Outside-of-litigation Dr. Chung is not alone. It is generally accepted that neurodevelopmental disorders such as ASD and ADHD result from an interaction *between* genes and environmental factors. *See* Ex. 8, Cabrera Rebuttal Rep. at 2–6. Just ask Defendants' other experts. Ex. 93, Faraone (2021) at 794 (emphasis added) ("[G]enes and their interaction with the environment *must* play a substantial role in causing ADHD."); Ex. 28, Kolevzon Dep. Tr. at 368:11–17 (discussing a 2021 paper by Dr. Kolevzon describing "[t]he etiology of ASD" as "multifactorial" including "genetic and environmental factors, as well as their interaction"); Ex. 49, Kolevzon Blog (2018) at 3 (stating that environmental factors such as "exposure to several toxins during pregnancy" can "act on genetic vulnerability to increase the risk of ASD").

Once again, Defendants resort to the heritability fallacy, pretending that if ASD or ADHD is 80% *heritable* that means it is 80% *inherited* (due to genes only and not the environment). *See, e.g.*, Defs. ASD Br. at 7; Defs. ADHD Br. at 6, Dkt. 1162. It is not only Plaintiffs' experts who

[6] *See* Ex. 194, SPARK Presentation (Feb. 21, 2017) at 5. As detailed in Plaintiffs' Memorandum in Support of the Rule 702 Motion to Exclude Dr. Wendy Chung, Dr. Chung gave this presentation in 2017 but included substantively the same slide in a presentation from April of this year. *See* Dkt. 1138 at 16–19.

dispute that fundamental misapplication of basic science. Ex. 8, Cabrera Rebuttal Rep. at 3–4; Ex. 1, Baccarelli Rep. at 39. Foundational textbooks instruct students of genetics not to make the mistake Defendants are peddling to this Court. *See* Ex. 185, Moore & Shenk at 1; Ex. 26, Chung Dep. Tr. at 297:16–298:20 (pointing to Emery & Rimoin as a "standard genetic textbook[]" that purportedly supports her opinion); Ex. 198, Emery & Rimoin at 401 (noting in the latest edition, "focusing on heritability loses a lot of information and is not recommended"). So do the National Institutes for Health. *See* Dkt. 1138 at 13–14 (describing NIH's publications on the "well-recognized" gene–environment interactions involved in ASD/ADHD).)

It is simply a fact: genetic factors are not the only cause of neurodevelopmental disorders, and environmental factors play a causal role. *See generally id.* at 13. As Dr. Cabrera cogently explained, "[t]he modeling of gene-environment interactions is common in the field of genetics," and "[u]nderstanding and applying this model, the objective and literal textbook answer-conclusion should be, that a monozygotic concordance rate [*i.e.*, rate at which a trait is expressed in both identical twins] that is less than 98-100% means that environmental factors influence the phenotype." Ex. 8, Cabrera Rebuttal Rep. at 3.[7] Illustrating the point for ASD and ADHD specifically, Polderman reported "twin correlations [for ASD and ADHD] by dimension range from .31-.40, which leaves *considerable* room for environmental and unknown factors." *Id.* at 4 (emphasis added); *see also* Ex. 186, Polderman (2014) at 4.

Defendants waive away the environment side of the gene by environment interplay because Dr. Cabrera offers specific evidence that APAP, the environmental factor, interacts with genes, the basic units of inheritance, to cause neurodevelopmental disorders like ASD and ADHD. *See* Ex.

[7] In Dr. Chung's Ted Talk, she presents a 77% concordance rate of ASD in monozygotic twins, which she then estimated to be 77-88% in her expert report, Ex. 14, Chung Rep. ¶ 55, all of which fall short of Defendants' heritability range cited in their brief. Regardless, even with these high heritability rates, environmental factors play a *causal* role. Ex. 8, Cabrera Rebuttal Rep. at 3.

3, Cabrera Report at 176–78. Gene expression analyses in living human brains or human embryonic-fetal brains is not ethically permissible; however, in vitro studies can measure APAP's impact on genes involved in neurodevelopment. In a peer-reviewed study that will be published in days, the authors used a "multi-omics approach"[8] to investigate the effects of APAP on the in vitro model of early human development. Ex. 179, Spildrejorde (2023) at 2.[9] The study exposed human embryonic stem cells undergoing neuronal differentiation with APAP concentrations corresponding to maternal therapeutic doses. *Id.* The authors concluded that "[o]ur data suggest that paracetamol may play a *causal* role in neurodevelopment." *Id.* This conclusion is consistent with Carter & Blizzard (2016), which analyzed gene by environment interactions with ASD using 206 autism susceptibility genes, and they found that the number of autism susceptibility genes targeted by APAP exceeded all other tested compounds besides valproic acid. Ex. 3, Cabrera Rep. at 176–77; Ex. 148, Carter & Blizard (2016) at 91–92 & fig.1.[10] It is therefore unsurprising that valproic acid is an environmental factor that Dr. Chung, but not Defendants' lawyers, recognizes as a likely cause of ASD. Ex. 57, Chung Ted Talk. Her blind spot for APAP is a pure creature of litigation.

B. Dr. Cabrera Properly Accounted for Genetic Confounding.

Without succumbing to the heritability fallacy, Dr. Cabrera candidly acknowledged the

[8] Dr. Cabrera explains that "[g]enetics and genomics have moved teratology and biological sciences towards '-omics' data over the last two decades," which includes "proteomics, transcriptomics, genomics, metabolomics, lipidomics, and epigenomics, which correspond to global analyses of proteins, RNA, genes, metabolites, lipids, and methylated DNA or modified histone proteins in chromosomes, respectively." Ex. 8, Cabrera Rebuttal Rep. at 1 n.1.

[9] As the parties advised the Court, Dkt. 1221, they agreed the recently accepted Spildrejorde (2023) is part of the *Daubert* record and on Dr. Cabrera's reliance list.

[10] Defendants misconstrue the Carter & Blizard (2016) results, stating that "[b]ecause the database included any reported interaction, regardless of type of study, or nature of the observed effect, the results say more about how often a compound had been the subject of research than anything else." Defs. Mech. Br. at 33-34. The Carter & Blizzard analysis, however, has nothing to do with frequency of reporting and rather focuses on chemical-genetic interactions through gene set enrichment analysis (GSEA). GSEA determines if sets of genes related to particular biological pathways or outcomes (e.g., ASD) are enriched with an exposure (e.g., APAP). Although enrichment requires underlying data, GSEA itself does not provide information on the frequency of research on a particular compound, as falsely claimed by the defense. Frequency reporting, as described by Defendants, would require a different database.

possibility of genetic confounding, and properly accounted for it. He relied upon epidemiological studies with negative controls, Ex. 8, Cabrera Rep. at 144–46, and concurred with Dr. Baccarelli's "analysis and conclusions," *id*. at 175, determining that such studies account for potential genetic confounding, Ex. 1, Baccarelli Rep. at 73.[11] Defendants' only answer is Gustavson (2021). It is not a very satisfying one. Dr. Cabrera devoted 1.5 single-spaced pages of his report analyzing Gustavson (2021), acknowledging "[i]n the sibling control model, the association between long-term acetaminophen use and ADHD in the child was no longer present." He also pointed out the limited study power and that the study authors themselves stated the "statistical power to detect within effects was relatively low." Ex. 3, Cabrera Rep. at 140; *see also id.* at 140–41, 147, 148. Dr. Cabrera had good grounds for not giving dispositive weight to a single, dramatically underpowered result that the study's own authors cautioned three separate times.[12] He explained those grounds in his report. Defendants' true objection is not that Dr. Cabrera ignored genetics, but rather that he refuses to testify in their favor. Rule 702 emphatically overrules that objection. *See In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 173 (S.D.N.Y. 2009).

III. Dr. Cabrera Properly Considered the Limitations of Each Relevant Study.

Rather than attacking Dr. Cabrera's methodologies, Defendants attempt to pick apart the underlying studies and argue that Dr. Cabrera "ignore[d]" unfavorable studies or failed to account for study limitations. *See* Defs. ADHD Br. at 19–24; Defs. ASD Br. at 27–38. Not so. Rather, as detailed *supra* at 5–8, Dr. Cabrera painstakingly analyzed the relevant epidemiological, Ex. 3, Cabrera Rep. at 128–68, preclinical, *id.* at 73–95, mechanistic, *id.* at 38–73, and APAP toxicity

[11] Plaintiffs refer to the Baccarelli Opposition for an in-depth discussion of the use of negative controls in the relevant epidemiological literature. *See* Baccarelli Opp'n at 12–14.

[12] *See* Ex. 52, Gustavson (2021) at 8 ("As only discordant siblings contribute to information in sibling control models, even the current very large birth cohort provided limited statistical power."); *id.* at 5 ("[T]he finding of similar risk for ADHD in siblings discordant for long-term maternal acetaminophen must be interpreted with caution and needs to be replicated in other studies."); Ex. 80, Gustavson Supp. Information at 7 ("These numbers show that statistical power to detect within effects was relatively low. Hence, these results should be interpreted with caution.").

studies, *id.* at 29–31, and outlined strengths and limitations for each. To quantify, that is 95, single-spaced pages summarizing and assessing the relevant literature.[13] Defendants' argument that he failed to consider certain evidence is really a veiled attack on the merits. Plaintiffs address many of these arguments below, but since Defendants lodged the same attacks on the science across experts, Plaintiffs also incorporate their Baccarelli Opposition.

A. Dr. Cabrera Reliably Considered All Epidemiological Studies and Their Limitations.

Dr. Cabrera went through the relevant epidemiological literature and summarized each study along with limitations, results, and the authors' conclusions. Ex. 3, Cabrera Rep. at 128–68. That is certainly sufficient under Rule 702. For Baker (2020), for example, Dr. Cabrera did not ignore the study's "shortcomings," Defs. ADHD Br. at 21, but stated that "[m]econium can identify drug exposure in the 2nd and 3rd trimester and reveal the relative concentration compared to others in the cohort, but cannot by itself identify exact dose or duration." *See* Ex. 3, Cabrera Rep. at 138 (detailing limitations of Baker (2020)). And as Defendants conceded, Dr. Cabrera acknowledged the "potential for residual confounding" in his report. Defs. ASD Br. at 21; Ex. 3, Cabrera Rep. at 138, and further elaborated in his rebuttal report that the risk of "residual confounding is always present, even in the most well-designed observational studies," but one can draw conclusions based on the "totality of longitudinal evidence." Ex. 8, Cabrera Rebuttal Rep. at 8; *see also* Ex. 25, Pinto-Martin Dep. Tr. at 270:8–15 ("Q. No matter how good your study is, it's always possible that there's some confounder out there that's actually driving the results. Is

[13] To put it into perspective, Dr. Powell fully describes and analyzes only *two* of the 99 studies identified in his literature search—Saad 2016 and Baker 2023, Ex. 18, Powell Report ¶¶ 67–70, and identifies the "[c]ritical [f]laws" that undermine the "[r]emaining [p]ublications" using primarily string citations to end notes that reference the other 97 studies. *Id.* at 29, 33; Ex. 30, Powell Dep. Tr. at 86:11–16. Powell testified that, for someone to figure out his analysis of the remaining publications, "I expect someone who is replicating what I've done to read the papers and decide for themselves what they feel is relevant." *Id.* at 107:2–18.

that true? A. Absolutely true."). Dr. Cabrera did not base his causal conclusion on Baker (2020) alone, but on the totality of evidence, as informed by his Bradford Hill analysis and WoE methodology.

Defendants similarly criticize Dr. Cabrera's treatment of Ji 2020 and Liew 2016, but Dr. Cabrera expressly acknowledged those studies' limitations. Defs. ASD Br. at 28–32; Defs. ADHD Br. at 20–22. For Ji 2020, Dr. Cabrera stated that "[t]he study excluded confounding by indication but was unable to exclude the potential residual confounders of genetic and environmental factors." Ex. 3, Cabrera Rep. at 132. For Liew (2016), Defendants take issue with Dr. Cabrea's *conclusion*, but concede that he acknowledged and analyzed the limitations of the paper, Defs. ASD Br. at 32, as they must, because Dr. Cabrera included *all* of the results in his report. *See* Ex. 3, Cabrera Rep. at 131. That Defendants ultimately disagree with his interpretation of the data is best reserved for cross examination and does not render his methodology unreliable. *See In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d at 209 (holding that where "the parties are simply interpreting the data differently" and the "conclusions are sufficiently reliable to be admitted," cross examination is the proper tool to expose purported flaws in an expert's analysis).

B. Dr. Cabrera Did Not "Cherry Pick" the Studies.

Defendants accuse Dr. Cabrera of "cherry-picking" the relevant evidence that showed no association, but far from "brush[ing] [these studies] aside without scientific justification," Defs. ASD Br. at 33, Dr. Cabrera provided extensive analyses for his weightings. Defendants argued that Dr. Cabrera ignored "Ji 2018, Saunders 2019, and Hornig 2018" and that those studies "***showed no statistically significant association***," Defs. ASD Br. at 33 (emphasis in original), but as set forth in Plaintiffs' Baccarelli Opposition, these studies showed no such thing. Baccarelli Opp'n at 37–39. Still further, Dr. Cabrera extensively analyzed Ji (2018), including its limitations, *and* that it showed an association, just not a significant one. Ex. 3, Cabrera Rep. at 139 ("However,

there were no significant associations between maternal plasma levels of acetaminophen metabolites and the risks of ASD diagnosis and other DD diagnoses.").[14] He did the same with Saunders (2019). *Id.* at 131–32 (stating that "[o]verall the study found that there was no statistically significant association between APAP use during pregnancy and a later diagnosis of ASD in children" but noted that the study authors themselves stated that "[w]ithout controlling for [socioeconomic status], the current model cannot fully account for all variables in the complex diagnosis of ASD.") Although Dr. Cabrera did not address Hornig, that study addressed prenatal fever, not APAP and ASD or ADHD. Ex. 81, Hornig (2019). It is certainly not patently unreliable that Dr. Cabrera did not consider that study on point.

The same is true for the ADHD studies that Defendants wrongly accuse Dr. Cabrera of "cherry picking." Once again, Dr. Cabrera included extensive write-ups of each study, including limitations. *See* Ex. 3, Cabrera Rep. at 141–42 (Liew (2014)); *id.* at 157–58 (Tovo-Rodriguez (2018)); *id.* at 159–69 (Vlenterie (2016)); *id.* at 162–63 (Parker (2020)). It is Defendants who seem to be cherry-picking what they highlight in their analysis. For example, the Liew (2014) authors reported that they had "adjusted for several indications" and that the results did not differ. Ex. 44, Liew (2014) at 319. They then ultimately concluded that "we found that prenatal exposures to acetaminophen may increase the risk in children of receiving a hospital diagnosis of HKD or ADHD medication and of exhibiting ADHD-like behaviors, with higher frequency increasing risk in an exposure-response manner." *Id.*[15] It is not cherry-picking for Dr. Cabrera to agree with the

[14] Critically, Ji (2018) measured APAP levels in the mother's blood *after* she delivered the child, providing a highly imperfect proxy for in utero APAP exposure. *See generally* Baccarelli Opp'n at 39.

[15] Although Defendants now try to undermine the Liew (2014) study, [redacted]

study authors' own conclusions that Defendants conspicuously ignore.

C. Dr. Cabrera's Analysis Is More Critical of Contrary Studies Than Defendants' Experts.

Surely Defendants do not think their own experts engaged in the methodological errors they accuse Dr. Cabrera of committing. It follows that if Dr. Cabrera was more rigorous and transparent than Defendants' experts, he should waltz through the *Daubert* gate. He was. Take the Brandlistuen study, which shows a positive association between prenatal use of APAP and cognitive, motor, and language skills in early childhood. Ex. 51, Brandlistuen (2013) at 1710. Dr. Pinto-Martin noted the authors' limitations of a "relatively low participation rate in MoBA (selection bias); assessment by self-report; does information not reported; potential residual confounding" as well as her own limitations of "non-diagnostic outcome; misclassification bias due to exposure through maternal report." Ex. 13, Pinto-Martin Rep. App'x 1 at 7. Dr. Cabrera acknowledged these same limitations *and* stated "[t]here was also a possibility of residual confounding factors, such as unreported infections or illness, influencing the observed effects. Ex. 3, Cabrera Rep. at 152. Other examples abound. *See also* Ex. 13, Pinto-Martin Rep. App'x 1 at 25 (detailing limitations of Vlenterie (2016); Ex. 3, Cabrera Rep. at 160 (detailing further limitations with Vlenterie (2016)); Ex. 16, Kolevzon Rep. ¶¶ 99, 115–16 (detailing limitations with Brandlistuen); Ex. 3, Cabrera Rep. at 152 (detailing further limitations with Brandlistuen); Ex. 16, Kolevzon Rep. ¶ 99 (detailing limitations with Stergiakouli); Ex. 3, Cabrera Rep. at 157 (detailing further limitations with Stergiakouli); Ex. 16, Kolevzon Rep. ¶¶ 99, 116 (detailing limitations with Tovo-Rodrigues); Ex. 3, Cabrera Rep. at 158 (detailing further limitations with Tovo-Rodrigues); Ex. 15, D'Alton Rep. at 41, 43, 47 (detailing some limitations with Liew (2014)); Ex. 3, Cabrera Rep. at 141 (detailing further limitations with Liew (2014)). Dr. Cabrera took more care than Defendants to point out limitations in the very studies that support his conclusions. That sound

scientific discipline is grounds for commendation, not exclusion.

IV. Dr. Cabrera Properly Considered Animal Studies.

[redacted] Defendants now say it is per se unreliable to evaluate animal studies and that Dr. Cabrera unreliably analyzed them. Both arguments fail.

A. Dr. Cabrera Reliably Looked to Animal Studies.

Defendants argue that Dr. Cabrera does not "articulat[e] a reliable basis for extrapolating from the animal data . . . to the diagnosis of ASD" or ADHD "in humans." Defs. ASD Br. at 63; Defs. ADHD Br. at 53–54. But the animal models are not a diagnostic tool. They are routinely used in the scientific community to determine how toxic exposures might contribute to the development of symptoms associated with disorders in humans. Dr. Cabrera does not merely "opine generally about the utility of animal studies." Defs. Mechanism Br. at 15. He explains their importance to determining APAP's developmental neurotoxicity at length and with specificity.

Although it would certainly be "useful to conduct carefully controlled studies using human subjects," there is no ethical way to do so "when a drug is suspected of causing a serious adverse outcome." Ex. 3, Cabrera Rep. at 76. No defense witness disagrees. *See, e.g.*, Ex. 30, Powell Dep. Tr. at 42:21–43:3; [redacted]

Humans and rodents share "underlying architecture in all regions of the brain." Ex. 3, Cabrera Rep. at 76–77. We "share common neurotransmitters, including serotonergic and endocannabinoid systems that both affect fetal brain development," and "common growth and

neurotrophic factors, such as brain-derived neurotrophic factor (BDNF)." *Id*. at 77. Both humans and rodents are "susceptible to cellular and DNA damage from superoxides or free radicals, such as NAPQI, and both produce glutathione as the main antioxidant in the brain and body." *Id.* As Dr. Cabrera explains, animal studies show that prenatal exposure to APAP, even at doses therapeutic to humans, can affect several shared regions associated with the development of ASD and ADHD. *See id*. at 65 ("Numerous animal studies have demonstrated that exposing developing brains to APAP at dosages equivalent to or less than the recommended therapeutic dosage in humans causes changes in key structures in the brain consistent with the impact of acetaminophen and its metabolites on oxidative stress, the endocannabinoid system, and prostaglandins."). Animal models can thus provide relevant and reliable evidence of the biological mechanisms by which prenatal APAP exposure may cause ASD and ADHD in human offspring.

Defendants cannot and do not contest that animal studies are commonly relied upon as evidence of drug toxicity in humans. [redacted] After the publication of the Consensus Statement, [redacted] *See* Pearson Opp'n at 10–17. FDA is also reviewing animal models of APAP's neurotoxicity. *See id*. And animal studies are already the cited basis for pregnancy warnings attached to other drugs that contain APAP. The FDA-approved label for Ultracet, a prescription painkiller produced by Janssen Pharmaceuticals (a Johnson & Johnson Company), discusses developmental studies in rats and mice specific to APAP before explicitly instructing doctors: "*Based on animal data*, advise pregnant women of the potential risk to a fetus." Ex. 189, Ultracet Label § 8.1 (emphasis added); *see also* Ex. 3, Cabrera Rep. at 120–22 (discussing labels for Ultracet and Ofirmev, another drug that contains APAP with a label that discusses animal studies of fetotoxicity).

Although courts have observed that "extrapolation from animal studies to humans entails some risks," it has never held, contra the scientific establishment, that results from animal studies *cannot* be extrapolated to humans. *Daniels-Feasel*, 2021 WL 4037820, at *13 (quotation marks omitted). The court's concerns over animal data in that case stemmed from "overwhelming contradictory epidemiological evidence" and the unreliable methodologies of the experts who relied on the animal data. *Id*. at *14, **18–19. Where, as here, the weight of the animal and epidemiological data align and an expert reliably considers that data, neither concern exists. Nor was Dr. Cabrera, as Defendants suggest, excluded from testifying in the *Zoloft* litigation. *See* Defs. Mechanism Br. at 15. The court allowed his testimony on biological mechanisms, noting that, as here, "he did not ignore the findings of those [animal] studies from which conclusions at odds with his opinion were drawn; rather he analyzed those studies and explained why those studies did not alter or undermine his own opinion regarding a plausible biological mechanism of injury." *In re Zoloft Prod. Liab. Litig.*, 26 F. Supp. 3d 466, 470 (E.D. Pa. 2014).

Dr. Cabrera's review of animal studies is further in line with the general guidance for evaluating a compound's teratogenicity, which "generally includes," and typically starts with, "one or more in vivo studies." Ex. 190, Toxicity Guidance at 5; *see also* Ex. 3, Cabrera Rep. at 13–15. To be sure, differences between humans and animals must be accounted for. Dr. Cabrera fully acknowledges as much. Ex. 3, Cabrera Rep. at 13, 77. But teratogenic "inferences" from these studies are still "of a kind that physicians and scientists reasonably"—and commonly—"make from good but inconclusive science." *Daniels-Feasel*, 2021 WL 4037820, at *14 (quotation marks omitted). Given the unavailability of human biological data on APAP's developmental neurotoxicity and the extensive animal data on APAP's developmental neurotoxicity, it was appropriate and necessary for Dr. Cabrera to evaluate animal studies. Excluding those studies and

Dr. Cabrera's analysis of them would deprive the factfinder of evidence that is routinely used by conscientious scientists, regulators, and Defendants themselves.

B. Dr. Cabrera Reliably Analyzed the Animal Studies.

Dr. Cabrera reviewed the animal studies reliably. Once again, Defendants have no argument with the WoE methodology that he used. That methodology, based on guidance from the OECD and other sources, is indisputably reliable. *See* Pearson Opp'n at 10–17 ([redacted]).

Defendants thus turn to their playbook favorite: cherry-picking.[16] *See* Defs. ASD Br. at 65–66. But he does nothing of the sort, as Defendants' few purported examples only serve to prove. Dr. Cabrera accurately reports the Klein (2020) study's conclusion that APAP is a developmental neurotoxicant while, as Defendants acknowledge, also reporting certain findings within that study that did not support that conclusion. Ex. 3, Cabrera Rep. at 102. He likewise does not "ignor[e]," but specifically reports, that the Gould (2012) study found that APAP exposure increased social activity in certain mouse strains, and he explained why this study and others support the conclusion that APAP exposure causes behavioral alterations consistent with ASD and ADHD. Defs. ASD Br. at 67; *see* Ex. 3, Cabrera Rep. at 83, 127; Pearson Opp'n at 23–25 (explaining why any observed change from the baseline is relevant evidence of neurotoxicity).

Defendants criticize Dr. Cabrera's treatment of Saad (2016). *See* Defs. ADHD Br. at 56. There were four findings in the behavioral analysis with $P<0.05$, but the authors set $P<0.008$ as the statistically significant threshold. Ex. 3, Cabrera Rep. at 83–84. Based on the American

[16] Defendants accuse Drs. Pearson and Cabrera of cherry-picking most of the same studies, so Plaintiffs refer to the arguments in their Pearson Opposition at 22–28, but note that Dr. Cabrera also provided detailed analyses for these animal studies. *See* Ex. 3, Cabrera Rep. at 102 (analyzing Rigobello (2021)); *id.* at 101–02 (analyzing Saeedan (2018)); Ex. 12, Cabrera Supp. Rep. (analyzing Klein (2023)).

Statistical Association guidelines, Dr. Cabrera explained that, "[r]egarding effect size, [s]tatistical significance is not equivalent to scientific, human, or economic significance. Smaller p-values do not necessarily imply the presence of larger or more important effects, and larger p-values do not imply a lack of importance or even lack of effect." *Id.* at 84. He concluded that "[b]ased on these principles, the results from this study that show P<0.05 but not P<0.008 should be interpreted under larger p-values do not imply a lack of importance or even lack of effect." *Id.*

And Defendants do not dispute that the Harshaw & Warner study found significant effects from APAP exposure on repetitive and social behavior, as the authors themselves concluded. *See* Ex. 191, Harshaw & Warner (2022) at 10. Defendants further criticize Dr. Cabrera for citing Motawi (2019), a study on adult rodents. *See* Defs. Mechanism Br. at 24. That criticism is misplaced; adult-rodent studies can show a given mechanism at work, as seen in Dr. Cabrera's report. *See* Ex. 3, Cabrera Rep. at 108–09.

V. Dr. Cabrera Reliably Applied the Bradford Hill Framework to Reach His Causation Opinion.

After undertaking a study-by-study review of the preclinical and epidemiological studies, *and* applying WoE methodologies to those studies, Dr. Cabrera applied the Bradford Hill factors to that evidence and concluded that "[t]herapeutic dosages of APAP taken by pregnant woman are sufficient to cause neurotoxicity, neurodevelopmental disorder, ASD, and ADHD in exposed offspring." Ex. 3, Cabrera Rep. at 196. Defendants embrace the Bradford Hill factors as a reliable methodology, *see, e.g.*, Ex. 13, Pinto-Martin Rep. at 53–66; Ex. 19, Faraone Rep. ¶ 168, but take issue with Dr. Cabrera's ultimate conclusion. Defendants' hollow attacks fly in the face of generally accepted science or the Bradford Hill factors themselves. At bottom, "scientists reliably applying the Bradford Hill factors may reasonably come to different conclusions about whether a causal inference may be drawn," *In re Abilify (Aripiprazole) Prod. Liab. Litig.*, 299 F. Supp. 3d

1291, 1307 (N.D. Fla. 2018), and Dr. Cabrera's Bradford Hill analysis simply reached a different conclusion than the one Defendants seek.

A. Dr. Cabrera Properly Considered ASD and ADHD as Part of His Bradford Hill Analysis.

Defendants contend that Dr. Cabrera improperly considers "proxy" studies that do not use ASD and ADHD clinical diagnoses as endpoints and generally conflates ASD and ADHD in his Bradford Hill analysis. Defs. ASD Br. at 38–43; 45–48; ADHD Br. at 31–37. As detailed in Plaintiffs' Hollander Opposition, Dr. Cabrera's approach is generally accepted by the scientific community. Hollander Opp'n at 6–20; *see also* Ex. 8, Cabrera Rebuttal Rep. at 1–6; *id.* at 3 (citing Ex. 186, Polderman (2014) for the proposition that "both genetic and environmental factors [ ] influence overlapping dimensions of ADHD and ASD);" *id.* at 4 (citing Ex. 192, Satterstrom (2019) at 2, which concluded that "ASD and ADHD have a similar burden of rare protein-truncating variants in evolutionary constrained genes, both significantly higher than controls. This motivates a *combined analysis* across ASD and ADHD" and identifying 15 common genes among the disorders with protein truncating variants). Even if this criticism were valid (it is not), Defendants conveniently ignore that Dr. Cabrera *separately* analyzed the literature concerning (1) ASD, (2) ADHD, (3) impaired learning, cognitive, or social outcomes, (4) birth outcomes, (5) meta-analyses, and (6) other relevant reviews and applied separate weight of evidence analyses to those buckets of evidence. *See* Ex. 3, Cabrera Rep. at 128. Defendants' attacks on Dr. Cabrera's approach does not undermine his independent conclusions.

B. Dr. Cabrera Reliably Applied the Bradford Hill Factors.

The scientific literature evidences an association between APAP and ADHD. On that, at least, the parties agree. But Defendants cannot even concede an *association* with ASD. Defs.

ASD Br. at 47–48. As set forth in Plaintiffs' Baccarelli Opposition, that simply blinkers objective reality. Baccarelli Opp'n at 33–42.

Defendants generally lodge the same attacks against Dr. Cabrera's Bradford Hill analysis as they do against Dr. Baccarelli' s analysis, and Plaintiffs incorporate the arguments asserted in their Baccarelli Opposition at 48–58, which summarily dispose of Defendants' arguments. Dr. Cabrera reliably applied the Bradford Hill factors of strength of association, Ex. 3, Cabrera Rep. at 189–90; consistency, *id.* at 190–91; biological gradient (dose response) *id.* at 191; specificity, *id.*; and temporality, *id.* Plaintiffs further outline Dr. Cabrera's reliable application of the plausible biological mechanism, coherence, analogy, and experiment factors.

1. Plausible Biological Mechanism

Defendants say that Dr. Cabrera failed to articulate a plausible biological mechanism—by which they mean a definitive biological mechanism—and then claim this failure is dispositive. Defs. Mechanism Br. at 1 ("Biological plausibility is necessary—but not sufficient—to establish general causation."); *see also* Ex. 19, Faraone Rep. ¶ 168(f) (opining that there is "no definitive description of any pathological mechanism that explains the onset of ADHD"); Ex. 31, Faraone Dep. Tr. at 121:10–17 (saying he "interpret[ed] the word 'plausible' to mean probable").[17] Both arguments are flat wrong. "The concept of biological plausibility…asks whether the hypothesized causal link is credible in light of what is known from science and medicine about the human body and the potentially offending agent." *Milward v. Acuity Specialty Prod. Grp., Inc.*, 639 F.3d 11, 25 (1st Cir. 2011). Dr. Pinto-Martin agrees. Ex. 25, Pinto-Martin Dep. Tr. at 542:22–25 (testifying

[17] JJCI attempted the same strategy in the Talc MDL. *See In re: Johnson & Johnson Talcum Powder Prods. Marketing, Sales Practices and Prods. Liab. Litig.*, MDL Dkt. 2738 (D.N.J.) Dkt. 9736-1. The court rejected JJCI's distortion of basic epidemiological precepts, holding that "biological plausibility does not require certainty or even proof for the biological mechanism in question" and that "[c]ontrary to Defendants' position, the fact that the mechanism has not been proven does not negate the reliability of the experts' opinion on this issue." *Id.* at 174–75.

that "plausible" means "possible"). And aside from temporality, *no* Bradford Hill factor is necessary to make a causal inference. Baccarelli Opp'n at 29.

Properly defined as credible or possible, Dr. Cabrera identified multiple biologically plausible mechanisms by which APAP can cause ASD and ADHD. Specifically, he undertook an AOP where he outlined "a causal pathway initiated by (1) molecular interactions, on to (2) cellular events, to (3) tissue and organ events, to (4) effects on the organism phenotype and behavior." Ex. 3, Cabrera Rep. at 38; *see id.* at 38–67 (detailing the causal pathway in twenty-nine, single-spaced pages with supporting authority).[18] He did this for oxidative stress and endocannabinoid effects (and also demonstrated that effects on prostaglandin, serotonin, and BDNF can contribute), and as set forth in Plaintiffs' Pearson Opposition, these mechanisms are well-known. *See* Pearson Opp'n at 10–17.

Defendants attempt to discredit Dr. Cabrera's reliance on AOP 20, but what they cannot dispute is that the AOP ***identifies APAP as a "chemical stressor" that can cause "oxidative stress" during "brain development" sufficient to disrupt "the establishment of neuronal connections and networks," and result in "functional impairment."*** Ex. 3, Cabrera Rep. at 35–36; Ex. 184, AOP 20 at abstract & 42.[19] To deflect, Defendants focus on the fact that AOP 20 specifies that oxidative stress can "lead to functional impairment in learning and memory" but did not specify ASD and ADHD. *See* Defs. Mechanism Br. at 7, 27–28. That is of no moment. First,

[18] In direct response to Dr. Chung's assertion that she was "not aware that the referenced biological pathways are established or accepted by the medical and scientific community as causal mechanisms for ASD and ADHD," Dr. Cabrera wrote: "I have referenced published adverse outcome pathways (AOPs) in my expert report. These include "Binding of electrophilic chemicals to SH(thiol)-group of proteins and /or to seleno-proteins involved in protection against oxidative stress during brain development leads to impairment of learning and memory" and "Adverse Outcome Pathway on chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities." Consistent with the pathways, is also the computational model presented by Vargason et al (2017) examining the enzymes in the methionine cycle and transsulfuration pathways, the latter of which produces GSH, as models of determining ASD and neurotypical metabolic differences." Ex. 8, Cabrera Rebuttal Rep. at 15–16.

[19] Notably, the other stressors identified other than APAP are chloroform and furan. Ex. 184, AOP 20 at 42.

Dr. Cabrera explained that he appl[ied] that AOP to see if there [are] any gaps in the mechanism for understanding whether there's a biological plausibility." Ex. 22, Cabrera Dep. Tr. at 310:10–13; *see generally* Ex. 3, Caberra Rep. at 18. Second, and more importantly, it is generally accepted that oxidative stress can plausibly cause ASD and ADHD, Ex. 3, Cabrera Rep. at 67–68, Pearson Opp'n at 5–7. AOP 20 even states that "OS has been linked to neurodevelopmental diseases and deficits like autism spectrum disorder and postnatal coordination motor deficits." Ex. 184, AOP 20 at 185; *see generally* Ex. 199, Nishimura (2021) at 1 (describing "oxidative stress as a common key event in developmental neurotoxicity," as identified by "adverse outcome pathways" for neurodevelopmental disorders such as ADHD and ASD). The syllogism is simple: AOP 20 shows that APAP exposure during development can cause oxidative stress sufficient to disrupt neuronal connections and networks; the peer-reviewed scientific literature identifies such oxidative stress as a biologically plausible mechanism that induces ASD and ADHD; therefore, Dr. Cabrera concludes that there is a biologically plausible mechanism by which APAP causes ASD and ADHD. Defendants will be hard pressed to refute his exercise in basic logic. *See In re Ephedra Prods. Liab. Litig.*, 393 F. Supp. 2d 181, 189 (S.D.N.Y. 2005) ("[A]nalogy, inference and extrapolation can be sufficiently reliable steps to warrant admissibility so long as the gaps between steps are not too great."); Ex. 22, Cabrera Dep. Tr. at 308:21–312:19; *id.* at 326:16–327:1.[20]

Defendants also erroneously state that "none of the experts articulates a time period during pregnancy when ADHD or ASD purportedly develop, or when the fetal brain is supposedly

[20] Defendants attempt to limit the AOP 20's application by focusing on peer review comments that resulted in a removal from "autism" as specific consequence of oxidative stress along with learning and memory impairment in AOP 20. Defs. Mechanism Br. at 7, 28. But contrary to Defendants' representation, the authors did not remove autism based on coming to a separate conclusion that there is insufficient evidence that oxidative stress can cause ASD, but rather because the AOP was derived from AOP 17 which originally focused on "impairment, learning, and memory." The authors further affirmatively stated in response to the peer review comments that "Autism was the background." *See* Ex. 200, Cabrera Dep. Ex. 16 at 14.

vulnerable to the changes that they claim can cause ASD or ADHD." Defs. Mechanism Br. at 14. To the contrary, Dr. Cabrera specifically identified when he thought the fetus is susceptible to the neurodevelopmental disorders of ASD and ADHD. Ex. 3, Cabrera Rep. at 182–83 fig.34 ("[D]uring the fetal period [nine weeks to birth], the majority of organ development is complete, so functional defects or minor abnormalities are more likely from toxic exposures."); *see also* Ex. 22, Cabrea Dep. Tr. at 22:51–15 ([A]utism is a neurodevelopmental disorder. A teratogenic effect that occurs during its critical window of exposure, which includes development of the nervous system, and the development of the nervous system continues throughout gestation, both the second and third trimester. So throughout neurulation and neural development, that is the critical window of exposure. I think the time of most sensitivity would be during the second trimester of pregnancy."). In other words, Dr. Cabrera identified "when the fetal brain is supposedly vulnerable to the changes that [Plaintiffs] claim can cause ASD or ADHD." Defs. Mechanism Br. at 14.

2. Coherence

Defendants argue that because Dr. Cabrera cannot pinpoint precisely *when* and *how* APAP exposure causes neurodevelopmental harm, he cannot reliably conclude that a coherent cause-and-effect relationship exists at all. Defs. ASD Br. at 60–61; Defs. ADHD Br. at 50–51. But the coherence criterion does not require scientific certainty as to the timing and mechanism of a relationship in order to determine whether it "seriously conflicts" with known scientific facts. Ex. 69, Bradford Hill at 298. As Dr. Cabrera describes in his report, APAP is a known "stressor" that generates oxidative stress, which can lead to "adverse outcomes . . . seen across numerous body systems." Ex. 3, Cabrera Rep. at 192–93. He explained at his deposition that the fetal brain is most susceptible to assault from APAP "throughout neurulation and neural development" and "the

time of most sensitivity would be during the second trimester of pregnancy." Ex. 22, Cabrera Dep. Tr. at 23:19–24. A cause-and-effect relationship between prenatal APAP exposures and ASD/ADHD fits coherently alongside these scientific facts. Other scientists who have reviewed the literature agree. Ex. 37, Alemany (2021) at 1000.

3. Analogy

Dr. Cabrera analogized APAP to "other substances known to have neurodevelopmentally toxic effects during pregnancy, including Δ9-THC, mercury, and valproic acid." Ex. 3, Cabrera Rep. at 193. Defendants argue that Dr. Cabrera's analogies fail because he does not "provide any scientific basis." Defs. ASD Br. at 61; Defs. ADHD Br. at 53. That is plainly false. Dr. Cabrera explains at length the evidence on which he relies to form his conclusion regarding the analogy criteria. *See, e.g.*, Ex. 3, Cabrera Rep. at 50–51 (describing how APAP and THC "both interact with the endocannabinoid system," APAP metabolite AM404 binds to the same receptors, and the studies showing THC's association with ASD and ADHD); *id.* at 194 ("Both mercury and APAP are reported to cause oxidative stress."); *id.* at 176–77, 194–95 (discussing evidence that APAP and valproic acid both target a high number of "autism susceptibility genes" and are associated with neurodevelopmental disorders). This sufficiently supports Dr. Cabrera's reliable conclusion as to the analogy criterion.

4. Experiment

Dr. Cabrera determined that the experimental evidence criterion was satisfied based on the available animal model studies. Defendants' claim that only human experimental evidence can be considered in assessing the experimental evidence criterion—ignoring the fact that it would be highly unethical to conduct such experiments—is scientifically incorrect. It is valid to consider the extensive preclinical evidence involving APAP and neurodevelopmental dysfunction when

assessing this factor. *See* Ex. 63, Modern Epidemiology at 21 ("Experimental evidence may refer to clinical trials, to animal experiments, or to experiments on tissues."); *see also* Ex. 8, Cabrera Rebuttal Rep. at 6–7 (noting that the causal relationship between valproic acid and neurodevelopmental disorders was established based on animal experiments without any "human brain experiments"). Thus, Dr. Cabrera's conclusion as to experimental evidence is reliable.

CONCLUSION

For the foregoing reasons, the Court should deny Defendants' Rule 702 Motions to Exclude Dr. Cabrera.

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Respectfully submitted,

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